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entitled (54) ABSORBABLE SURGICAL SUTURE.

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7200/66 09.4; 70.8; 47.7; 40.5.

The following statement is a full description of this invention, including the best method of performing it known to us

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ARTICLES OF MANUFACTURE

This invention relates to new articles of manufacture and to their use. More particularly, the invention is concerned with articles prepared from polymers, including copolymers, of lactic acids and their use in surgical applications; e.g., sutures and other structures used in joining or supporting living tissues.

Catgut (actually from sheep intestine) is the most commonly used absorbable suture now on the market. In many instances, however, it causes adverse tissue reaction in the sutured flesh. This, together with the fact that it is expensive, nonuniform both in cross section and composition, and requires storage under moist conditions, makes it far from an ideal suture material. Nylon, stainless steel, cotton, linen, ramie, "Teflon" fluorocarbon resin, "Dacron" polyester fibers, silk, and other materials have been suggested and/or used as surgical sutures. Some of them have advantages over catgut in strength, uniformity and storage characteristics, but they are not absorbed by living tissue.

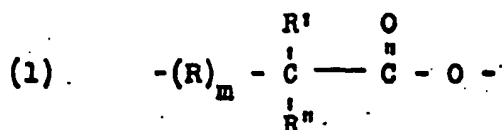
Among the requirements of the ideal absorbable suture product are that it should handle properly, should not create a situation favorable to bacterial growth, should have adequate tensile strength, should not tear flesh, should be controllably uniform in properties, including dimensional

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stability within the body, should be sterilizable, should be absorbable by living tissue, preferably at a constant rate regardless of the place in the body and the condition of the patient, without causing such unfavorable tissue reactions as walling off, granulation, excessive edema, etc., and finally should be capable of tying and holding surgical knots properly.

This invention fulfills the above requirements to a remarkable degree by providing highly oriented, high tenacity filaments of polymers and copolymers of lactic acid, the filaments having excellent dimensional stability in body tissue and preferably retracting less than 15% in an accelerative test in which the filaments are immersed in water at 77°C. for a period of five minutes.

These filaments are prepared from lactic acid polymers and copolymers having an inherent viscosity of at least 1, preferably above 1.2, as determined at 0.1% concentration in benzene by weight at 25°C. prior to being oriented. Any polylactide composition containing up to about 15%, and preferably up to about 10% to 12% by weight of repeating units of the formula



wherein R is lower alkylene, preferably methylene ( $-\text{CH}_2-$ ) or ethylene ( $-\text{CH}_2\text{CH}_2-$ ), m is 0 or 1, R' is hydrogen or lower alkyl, R'' is hydrogen or alkyl of up to about 22 carbons when m is 0 and hydrogen or lower alkyl when m is 1, and can be the same as R' or different, can be employed to make the sutures of this invention. Preferred, because of availability of starting materials, are repeating units derived from  $\alpha$ -hydroxycarboxylic acids, i.e., units of the

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above formula in which  $m$  is zero. Most preferred, because of the properties of the sutures made therefrom, are repeating or comonomer units derived from glycolide or DL-lactide, i.e., repeating units of formula (1) in which  $m$  is 0,  $R'$  is hydrogen or methyl, and  $R''$  is hydrogen. In other words, the number of carbon atoms in the repeating unit is 2 to about 24, preferably 2 to about 8, and most preferably 2 to 3. It will be understood that when  $m$  is zero,  $R'$  is methyl, and  $R''$  is hydrogen, the repeating unit in formula (1) could refer to DL-lactide which is a copolymer, or to the principal unit which would indicate that the polylactide composition is a homopolymer.

Illustrative of the comonomers which can be employed with the lactide to form copolymers useful in preparing the filaments of this invention, there can be named glycolide,  $\beta$ -propiolactone, tetramethylglycolide,  $\beta$ -butyrolactone,  $\gamma$ -butyrolactone, pivalolactone, and intermolecular cyclic esters of  $\alpha$ -hydroxybutyric acid,  $\alpha$ -hydroxyisobutyric acid,  $\alpha$ -hydroxyvaleric acid,  $\alpha$ -hydroxyisovaleric acid,  $\alpha$ -hydroxycaproic acid,  $\alpha$ -hydroxy- $\alpha$ -ethylbutyric acid,  $\alpha$ -hydroxyisocaproic acid,  $\alpha$ -hydroxy- $\beta$ -methylvaleric acid,  $\alpha$ -hydroxyheptanoic acid,  $\alpha$ -hydroxyoctanoic acid,  $\alpha$ -hydroxydecanoic acid,  $\alpha$ -hydroxymyristic acid,  $\alpha$ -hydroxystearic acid, and  $\alpha$ -hydroxylignoceric acid.

The filaments prepared from the above-described lactide polymers and copolymers are conveniently formed by melt-extruding the polylactic acid through a spinneret and then drawing the filaments in one or more stages to at least four times their original length to effect orientation and to improve their tensile strength. The resultant oriented

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filaments are strong and retain much of their strength on being tied into surgeon's knots.

To further improve their dimensional stability and particularly tensile strength retention, one may subject them to an annealing treatment. This optional annealing treatment is effected by heating the filament, while holding it essentially taut, at 60°C. to 150°C., and then allowing it to cool to room temperature (25°C.) while held taut. The annealing is preferably conducted for such a time that the filament shows less than 30%, most preferably less than 15%, shrinkage on subsequent immersion, for five minutes without tension, in water at 77°C. The heating step of annealing usually requires from 0.5 to 5 minutes.

A filament which meets the foregoing shrinkage test (77°C.) undergoes substantially no shrinkage when used as a suture in contact with body tissues (see Example II). The conditions of this test are designed to give a quick in vitro measure of the dimensional stability of the filaments that can be projected to their usefulness as suture materials. In this connection, it should be mentioned that the conditions of draw have an influence over the shrinkage. Further, it has been found that even those filaments showing a large amount of shrinkage at 77°C. have relatively little shrinkage at 37°C. (98.6°F.), i.e., at body temperature, even after being in contact with distilled water for 10 and 21-day periods.

Since the function of a suture is to hold severed tissue until healing is well along, and to prevent separation as a result of movement or exercise, the suture should have adequate strength. It is particularly important that strength be maintained when knots are tied and during the actual procedure of drawing tight a suitable knot. Catgut

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is well known to have marginal strength in this respect. In contrast, filaments from lactic acid homopolymers and copolymers in high molecular weight oriented form are exceptionally strong and most significantly retain a high proportion of their strength at the knot point, as shown in the following table:

TABLE I

	Tensile Strength (Straight Pull) (1)	% Elongation at Break	Tensile Strength (Surgeon's Knot) (5)	% Loss in Strength, Knot vs. Straight
Poly-L(-)-lactide	120,000 psi	17	85,000 psi	29
Poly-L(-)-lactide	100,000 psi	16	75,000 psi	25
Catgut	50,000 psi	20	29,000 psi	42
	44,000 psi	20	27,000 psi	39
L(-)-lactide/ $\gamma$ -butyrolactone (95/5) copolymer	59,000 psi	17	42,000 psi	29

- (1) Inherent visc. = 2.5, 10X draw; 0.006 inch diameter
- (2) Inherent visc. = 2.5, 10X draw, 0.005 inch diameter
- (3) Chrome gut, 3-0 size (0.008-0.010 inch diameter)
- (4) Chrome gut, 2-0 size (0.010-0.013 inch diameter)
- (5) After U. S. Pharmacopeia
- (6) Inherent visc. (bulk polymer) = 3.0 (spun filament = 1.6), 10X draw, 0.009 inch diameter

As will be apparent from Table I, the inherent viscosity of the spun filament, i.e., the oriented filament, may be somewhat less than that of the bulk polymer or copolymer, for during the drawing operation some degradation of the polymer may occur depending on the drawing conditions

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employed. If the sutures are sterilized by high energy radiation, there may be a further lowering of the molecular weight of the polymer. However, by starting with lactic polymers and copolymers having inherent viscosities of at least 1, the sutures prepared therefrom are entirely satisfactory even though there may be some loss in inherent viscosity due to extrusion and orientation, and possibly sterilization.

The filaments of this invention are further characterized by their hydrolysis behavior and absorbability. On treatment with boiling water for 100 hours, they lose at least 20, and preferably at least about 50%, of their weight. On treatment with boiling water for a period of 50 hours, the polymers and copolymers lose at least about 8% of their weight, and preferably they lose at least about 35% of their weight.

By varying the type and amount of comonomer employed, the rate of hydrolysis (absorption) of the suture can be controlled. In contrast to the highly variable absorption rates of catgut, the absorption of polylactide is relatively more independent of the place in the body where used and of the condition of the patient. Since the hydrolysis rate of a particular lactic acid copolymer is constant at a fixed temperature, say, at 37°C., absorption can be speeded up, for instance, by using different copolymers. For example, poly-L-lactide was 15.3% absorbed in the back muscle of a rat after 270 days. Under comparable conditions, L(-)-lactide/DL-lactide (97/3) copolymer was 18.5% absorbed, L(-)-lactide/DL-lactide (95/5) copolymer was 29.0% absorbed, L(-)-lactide/glycolide (95/5) copolymer was 27.3% absorbed, and chromed catgut was 67% absorbed.

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As already indicated, high tensile strength is an exceedingly desirable characteristic for suture materials. The filaments of the present invention are characterized by having a tensile strength of at least 25,000 psi, preferably above 40,000 psi. Some have tensile strengths ranging up to 100,000 psi and higher. Their knot strengths, expressed in pounds of pull, exceed the minimum limits set for absorbable sutures by the U.S. Pharmacopela, i.e., from 0.125 lb. for a 1-2 mil filament to 25 lbs. for a 36-40 mil filament.

In preparing the polymers and copolymers from which the filaments of this invention are made, the appropriate intermolecular cyclic ester or intramolecular cyclic ester (lactone) of the hydroxy acid is employed. These can be derived from pure D(-)- or L(+)-lactic acids, the optically inactive DL-lactic acid mixture, any desired mixtures of pure D(-)- and L(+)-lactic acids, and other alpha, beta, or gamma-hydroxy acids, about which more will be said later. In general, it is preferred, for the preparation of lactic acid homopolymers and for the introduction of lactide repeating units into copolymers to use as a starting material a lactide derived from either the pure L(+)-acid or pure D(-)-acid because the polymers obtained therefrom have a higher melting point than those derived from the DL-acid mixtures, are much less water-sensitive, are stronger, and have a greater degree of crystallinity. For example, the polylactides from the DL-acid melt at 130° to 140°C., whereas those from the L(+)-acid melt at 145° to 175°C. The polylactides from the L(+)-acid or D(-)-acid are less sensitive to alcohol, a commonly used sterile medium in surgery, than those from the DL-acid. The L(+)- form is more readily available than the D(-)-acid and hence is



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particularly preferred. It is to be understood that the various lactides can be made from the corresponding lactic acids by a variety of published methods including that described in Schneider U. S. 2,703,316.

Table II, below, summarizes data comparing the properties of polymers prepared from L(-)-lactide with those prepared from DL-lactide.

TABLE II

	<u>DL-lactide</u>	<u>Polymer from L(-)-lactide</u>
inherent viscosity	0.7-2.0	0.7-3.5
melting point	130-140°C.	145-175°C.
optical activity	no	yes (-186°)
thermally stable	yes	yes
solubility	CHCl <sub>3</sub> , benzene, acetone	CHCl <sub>3</sub> , benzene, acetone
density	1.26	1.26
tensile strength at break (monofilament)	20,000- 40,000 psi	70,000- 100,000
elongation at break (monofilament)	15-30%	15-30%
tensile strength at break (dry film)	26,000 psi.*	29,000 psi.*
inherent viscosity (film)	1.29*	1.27*
elongation at break (film)	48%*	23%*

In general, the tensile modulus, melting point, and specific rotation of lactic acid homopolymers decrease with increasing amounts of the antipode in the mixture.

\*Taken from U.S. 2,758,987

In some cases this is desirable because it leads to filaments which have improved flexibility, without appreciable sacrifice in strength.

In preparing copolymers, the repeating units derived from comonomers discussed above are introduced by use of the appropriate cyclic esters. For repeating units derived from alpha-hydroxy acids, these are usually the intermolecular cyclic esters containing six-membered rings, e.g., glycolide. For repeating units derived from beta- or gamma-hydroxy acids, the monomeric lactones, e.g., beta-propiolactone and gamma-butyrolactone, are usually used.

In preparing the filaments of this invention, it is essential to use polymers and copolymers made from highly purified lactides. For example, for excellent results L(-)-lactide should have a melting point of at least 96°C. and a specific rotation greater than -295°. The polymerization is effected by heating the lactide above its melting point, but below about 215°C. in the presence of a polyvalent metal oxide or compound thereof, under anhydrous conditions in an inert atmosphere.

Specially useful catalysts are zinc oxide, zinc carbonate, basic zinc carbonate, diethylzinc, titanium, magnesium or barium compounds, litharge, and the like.

The amount and type of catalyst used determine the particular temperature and time required to produce polymer useful for conversion to the filaments of this invention. Thus, the amount can be as low as 0.01 weight percent or as high as 2 weight percent. As a rule, the lower the amount of catalyst, the longer the time required to produce polymer of a given inherent viscosity and, conversely, the higher the catalyst concentration, the shorter the time. The best balance is usually obtained employing from 0.02 weight percent to 1 weight percent of catalyst.

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In general, it is desirable to agitate the reaction mixture continuously during the polymerization in order to produce a homogeneous polymer at good conversions and to conduct the reaction in two steps, the first being carried out at a lower temperature than the second, or finishing step. Other methods, such as those disclosed in U.S. Patents 2,703,316 and 2,758,987, can be used in making the polymers.

The following is a brief description of a method for preparing the polymer or copolymer useful for conversion to the filaments of this invention: Lactide, purified by several crystallizations from carbon tetrachloride, is placed either alone in the case of homopolymerization, or with one or more solid comonomers in case of copolymerization, in a thoroughly dried reactor equipped with a stirring bar, nitrogen inlet tube, and a drying tube filled conveniently with anhydrous magnesium sulfate or calcium chloride. Nitrogen, which has been dried by passage through anhydrous magnesium sulfate or calcium chloride, is introduced immediately above the reaction mixture and heating and stirring are started. When the temperature of the reaction mixture has reached about 100°C., the nitrogen inlet is replaced by a thermometer, and from about 0.01 to 2 weight percent of an oxide or salt, of Group II metal of atomic number 12 through 56, or litharge is added. In the case of copolymerization with a liquid comonomer the liquid comonomer is preferably added after the lactide has melted. Heating is continued until polymer having an inherent viscosity of at least 1 at 0.1% concentration in benzene at 25°C. is obtained. This may require from a few minutes up to 25 or more hours, depending upon the catalyst used.

Polymer, produced as above, may be suitably further treated by cutting it into small pieces, dissolved in a

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suitable solvent, for example, benzene, toluene, or xylene, and the polymer precipitated by pouring the solution into a large volume of a nonsolvent for the polymer, desirably hexane. The precipitated polymer is removed by filtration, transferred to a blender and a nonsolvent for the polymer is added. The blender is started and after a homogeneous dispersion has been obtained, the dispersion is filtered. The polymer is allowed to dry on the filter, and is then transferred to a vacuum oven. After drying overnight at 100°C., the polymer is removed from the oven and allowed to cool to ambient temperature.

As already indicated, the polymer material can be converted to filaments by melt-extrusion and also from solution. The diameter of the resulting filaments may be as small as 0.1 mil or less for the individual strands making up the multifilament structures and as large as 45 mils for very heavy monofilament sutures. Generally, however, the filaments of this invention will not have a diameter greater than 20-25 mils. Preferred are monofilaments having diameters of about 1-20 mils and multifilament structures having individual filaments of from less than 0.5 to 2 mils diameter.

It will be understood that spinning and drawing may be done singly or in multiples. To prepare multifilament braided sutures, one may take either monofilaments or groups of filaments to braid.

Spinnerets having orifice sizes of 5 mils or higher, say, up to 150 mils, are suitable for spinning monofils. In spinning from solution, the solution may be extruded either into an atmosphere heated to above the boiling point of the solvent or into a nonsolvent for the polymer, e.g., hexane.

After spinning, the polylactide homo- and copolymer filaments are drawn to effect orientation and to improve tensile strength. This is accomplished by drawing

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(permanently elongating) the filaments at a temperature between 70°C. and 140°C., preferably between 90°C. and 135°C. the preferred draw ratio being from 5:1 to 11:1. The drawing step may be conducted in one or more steps, in air or in a bath containing a liquid nonsolvent for the polymer, e.g., glycerol or water. This drawing brings about a marked increase in tensile strength and molecular orientation, as measured by the X-ray orientation angle.

Following the drawing, the filaments, particularly homopolylactide filaments, may be subjected to annealing. This is conveniently carried out by running the oriented filaments from a feed roll to a take-up roll and heating the filaments between the rolls, with the take-up roll rotating at a speed ranging from the same speed of the feed roll to a speed 4% slower than that of the feed roll. At the first mentioned speed ratio, essentially no shrinkage will take place, and at the second mentioned speed ratio shrinkage will take place up to 4% of its length. As a consequence of this annealing, the filaments undergo essentially no shrinkage under the action of body fluids, when used as sutures.

Instead of spinning the homo- or co-polylactide into filaments, it is possible to extrude or cast it into films, which are then drawn and annealed. The films thus treated can be cut into narrow strips for use as sutures. In the preferred embodiment the sutures are made from filaments.

It is to be understood that minor amounts of inert additives such as coloring materials and plasticizers can be incorporated in the sutures by being mixed with the preformed polymers and copolymers by known techniques. Any of a variety of plasticizers such as, for instance, glyceryl triacetate, ethyl benzoate and diethyl phthalate can be used to advantage, especially with poly-L-lactide. The amount of plasticizer may vary from 1-40% based on the weight of the polymer. Not only does the plasticizer render the filaments more pliable and

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more easy to handle, but it also helps in spinning. By the term "inert" is meant materials that are inert chemically to the polymer or copolymer, and are inert to living tissue, i.e., do not cause any of the adverse effects discussed on page 1 of this specification.

The present invention may be further illustrated by the following examples:

EXAMPLE I

Filaments having a diameter of 11.5 to 12.5 mils, a modulus of  $1.04 \times 10^6$ , tensile strength of 47,000 lb./sq.in. a knot strength of 37,000 lb./sq.in. and an elongation at break of 21%, were prepared by spinning polymer from L(-)-lactide, said polymer having an inherent viscosity of 2.44 (measured at 0.1% concentration in benzene at 25°C.), from melt at 190°C., and drawing to 6:1 ratio in glycerol at 95°C. Some of the filaments were annealed taut at 126°C. and others at 100°C. as shown in more detail in Table III which follows:

TABLE III

<u>Annealed Taut at 126°C. for 5 Minutes</u>	<u>Shrinkage</u>
Placed relaxed in oven at 126°C. for 5 minutes	7.4%
Control (i.e. not annealed)	28.2%
Placed relaxed in water at 100°C. for 5 minutes	13.0%
Control	28.2%
Placed relaxed in water at 77°C. for 5 minutes	1.4%
Control	18.0%
<u>Annealed Taut at 100°C. for 5 Minutes</u>	
Placed relaxed in oven at 100°C. for 5 minutes	11.0%
Control	21.4%
Placed relaxed in water at 77°C. for 5 minutes	7.4%
Control	18.0%

Annealed filaments such as described above are particularly useful as sutures as evidenced from Example II.

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EXAMPLE II

A polymer of L(-)-lactide, said polymer having an inherent viscosity of 1.4, was melt spun at 160° to 170°C. into a monofilament. The filament was then drawn to four times the undrawn length by passage over a metal plate heated to 90°C. The filament obtained measured 0.007 inch in diameter. To improve dimensional stability, the drawn monofilament was annealed for three minutes at 90-95°C. while under tension. The drawn, annealed filament was cut to convenient length and sterilized by being placed in polyethylene bags, which were sealed and exposed to two passes under a Van de Graaff beam of 2 million electron volts. Some of the bags contained dry monofilament, some contained monofilament in water and some contained monofilaments in ethyl alcohol.

The effect of annealing can be seen by these observations. When the annealed monofilament was heated in a dry oven at 95°C. for 3 minutes in a relaxed state, it shrank less than 4%. By contrast, an identical monofilament that had not been annealed shrank 25%. The annealed monofilament at 77°C. in water for 5 minutes shrank 14%.

In another experiment, the annealed monofilament was implanted in the abdominal cavity of a young adult male rat. After 16 days the implantation was removed. It had undergone less than 2% shrinkage.

The monofilaments thus obtained were used to connect severed muscle tissue in rats and in dogs in accordance with the following procedure:

A mid-line incision was made in the rat's abdominal skin, the skin was peeled back, and two small slits were then made in the abdominal muscles, one on either side of the mid-line. Each rat was sutured with several loops of

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the sterilized monofilaments prepared as above in one incision. Each rat had, as a control, either unchromed or chromed catgut suture in the other incision (size 4-0, 0.006-0.008 inch diameter). The skin was then closed and clamped. The rats were observed at regular intervals.

The sterilized monofilaments were tested for suturing dogs as follows: A mid-line incision about 3" to 4" long was made in the skin over the abdomen of a six-month old dog. The skin was separated from the abdominal musculature and retracted with conventional retractors. Three incisions about 1" long were made through the abdominal musculature. One incision was closed with polylactic acid suture material, the other incisions were sutured with commercial catgut sutures (U.S. Type A Plain, Size 4-0, and medium Size 4-0).

Rats were sacrificed at intervals of 2, 4, 7, 14, 28, 59, 91, and 140 days. Dogs were sacrificed at 14, 23, and 50 days. In these examinations it was observed that the polylactic acid monofilaments were more slowly absorbed than plain gut. Further, it was observed that there was less general tissue reaction with the polylactic acid, as shown by gross appearance and by examination of photomicrographs.

#### EXAMPLE III

Polymer from L(-)-lactide having an inherent viscosity of 3.11 and 0.1% concentration in benzene at 25°C., prepared by previously described methods, was converted to sutures by melt spinning, drawing, and annealing as described in Example I.

#### EXAMPLE IV

Monofilaments of poly-DL-lactic acid, having an inherent viscosity of 1.42 at 0.1% concentration in benzene at



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25°C., were tested as sutures after having been sterilized by two passages under a 2 mev electron beam at 1 to 1.25 Mrads per pass. The sterilized monofilaments were tested in suturing rats as follows:

A mid-line incision was made in the rat's abdominal skin, the skin was peeled back, and two small slits were then made in the abdominal muscles, one on either side of the mid-lines. Each rat was sutured with several loops of the sterilized monofilaments prepared as above in one incision and with a catgut suture as control in the other incision (unchromed, 4-0, 0.006-0.008 inch diameter). The skin was then closed and clamped. The rats were observed at regular intervals. After approximately one month, the poly-DL-lactic acid sutures were about 50% hydrolyzed, tissue reaction was minimal to absent with no evidence of granulation and adhesions. In the rats sutured with catgut, the catgut hydrolyzed to about 60% after about one month, but there was pronounced tissue reaction with evidence of adhesions and granulation.

After about 60 days both the polylactic acid and catgut sutures were absorbed, but the rats sutured with the catgut showed more scar tissue than the rats sutured with the polylactic acid.

With rabbits, the suture material was found to be completely hydrolyzed before about 38 days, irrespective of whether it was plain catgut or polylactic acid. However, the rabbits which were stitched with the polylactic acid sutures showed no adverse tissue reactions, with no tissue walling off or covering over of the suture material, in contrast to the behavior of catgut.

A mid-line incision about 3" to 4" long was made in the skin over the abdomen of a six-month old dog. The skin was separated from the abdominal musculature and

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retracted with conventional retractors. Two incisions about 1" long were made through the abdominal musculature. The right side incision was closed with polylactide suture material. The left incision was sutured with catgut (U.S. Type A Plain, Size 4-0). After four days the polylactide was intact with no evidence of granulation or adhesion. At the end of 14 days the dog was again examined and at the time the incision closed with the catgut showed intense inflammatory reaction. In contrast, the incision closed with the polylactic acid suture was free of granulation and the scar was clearly visible, i.e., no inflammation was evident. In both cases, however, the suture material had been absorbed by the tissue.

#### EXAMPLE V

A mixture of 95 parts of L(-)-lactide and 5 parts of DL-lactide was fused under nitrogen, and there was added 0.125 part of diethylzinc as a 25% solution in heptane. The mixture was heated at 105°C. for 1 hour at atmospheric pressure in an atmosphere of nitrogen. The solid L(-)-lactide/DL-lactide (95/5) copolymer thus obtained had an inherent viscosity of 2.63 (0.1% solution in benzene at 34.5°C.). The copolymer was ground to a fine powder, which was in turn pressed to a plug suitable for use in an extrusion-spinning apparatus. Filaments of the copolymer were spun at about 200°C. through a 35-mil spinneret and were drawn to 6.4 times their original length in glycerol at about 120° C. The drawn filaments had the following properties:

Inherent viscosity:	1.7
Diameter:	12.5 mils
Tensile strength:	58,500 psi
Elongation at break:	20%

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Modulus:	$1.08 \times 10^6$ psi
Knot strength:	37,000 psi
Shrinkage after 5 min. in water at 77°C.:	23%
Weight loss after 50 hrs. in boiling water:	39%

After 30 Days in Distilled Water at 37°C.:

Inherent viscosity:	0.55
Tensile strength:	19,000 psi
Weight loss:	2.6%

After 90 Days in Distilled Water at 37°C.:

Inherent viscosity:	0.38
Tensile strength:	5000 psi
Weight loss:	7.0%

EXAMPLES VI - XIII

A number of other lactide copolymers were prepared and spun into filaments by the method of Example V. When the comonomer was a liquid at ordinary temperature ( $\beta$ -propiolactone,  $\gamma$ -butyrolactone or pivalolactone), it was added to the lactide only after the lactide had been fused. The bulk-polymer properties, spinning conditions, and filament properties of these copolymers are summarized in the following table.

TABLE IV

EXAMPLES	VI	VII	VIII	IX	X	XI	XII	XIII
% Comonomer	7.5% DL-lactide	10% DL-lactide	15% DL-lactide	5% glycolide	10% glycolide	5% $\beta$ -propiolactone	5% $\gamma$ -butyrolactone	5% pivalolactone
Inh. viso. (bulk)	2.87	2.50	2.39	2.53	2.52	1.31	2.99	2.68
Spinning temp.	190°C.	205°C.	200°C.	210°C.	195°C.	-	170°C.	170°C.
Draw ratio	8.6	8.1	7.5	8.8	8.0	-	10	10
Drawing temp.	128°C.	125°C.	100°C.	125°C.	100°C.	-	115°C.	100°C.
Inh. viso. (drawn fil.)	1.75	1.75	1.47	1.84	1.70	-	1.73	1.64
Diameter (mils)	11.5	11.0	12.5	10.3	8.5	-	9.4	8.5
Ten. strength (psi)	53,300	69,000	53,000	77,000	27,500	-	59,000	78,000
Elong. at break	20%	20.7%	18.5%	14%	32%	-	17%	22%
Modulus (psi)	$1.4 \times 10^6$	$1.1 \times 10^6$	$1.1 \times 10^6$	$1.1 \times 10^6$	$0.46 \times 10^6$	-	-	$1.2 \times 10^6$
Knot strength (psi)	37,500	37,100	30,000	43,000	27,000	-	42,000	48,000
Shrinkage ( $H_2O/77^\circ C./5$ min.)	13%	27.5-44%	72%	12%	73%	-	ca. 15%	ca. 15%
Wt. loss ( $H_2O/100^\circ C./50$ hrs.)	44%	48%	65%	45%	-	-	-	-

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TABLE IV (continued)

EXAMPLES	<u>VI</u>	<u>VII</u>	<u>VIII</u>	<u>IX</u>	<u>X</u>	<u>XI</u>	<u>XII</u>	<u>XIII</u>
After 30 days in water at 37°C.:								
Inh. visc. (drawn fil.)	-	0.54	-	0.58	-	-	0.81	0.72
Ten. strength (psi)	-	23,800	-	26,000	-	-	-	-
Wt. loss	-	3.5%	-	7.4%	-	-	5.6%	0.3%
After 90 days in water at 37°C.:								
Inh. visc. (drawn fil.)	-	-	-	0.34	-	-	0.58	0.35
Ten. strength (psi)	-	-	-	12,000	-	-	-	-
Wt. loss	-	-	-	12.1%	-	-	7.1%	3.5%

Copolymers of L-lactide with the intermolecular cyclic esters of  $\alpha$ -hydroxybutyric acid and  $\alpha$ -hydroxyheptanoic acid were made by essentially the method of Example V.

A mixture of 44.2 parts of L-lactide and 5.8 grams of the cyclic ester of  $\alpha$ -hydroxybutyric acid was fused under nitrogen, and there was added 0.08 g. of 25% solution of diethylzinc in heptane. The mixture was heated at 105-108°C. for 3 hours at atmospheric pressure in an atmosphere of nitrogen. The resulting copolymer of L-lactide and the intermolecular cyclic ester of  $\alpha$ -hydroxybutyric acid (88.4/11.6) had an inherent viscosity of 2.15 (0.1% solution in benzene).

The copolymer of L-lactide and the intermolecular cyclic ester of  $\alpha$ -hydroxyheptanoic acid (90/10) was prepared similarly from 45 g. of L-lactide, 5 g. of cyclic ester, and 0.08 g. of 25% solution of diethylzinc in heptane. After the mixture was heated for 3 hours, the resulting polymer had an inherent viscosity of 2.28.

The spinning conditions and filament properties of these copolymers are summarized in Table V.

The intermolecular cyclic esters of  $\alpha$ -hydroxybutyric acid and  $\alpha$ -hydroxyheptanoic acid were prepared essentially by the method of Bischoff and Waloen, Ann. 279, 100 (1895). The sodium salts of the corresponding  $\alpha$ -bromo acids were made from the acids and sodium methoxide in an ethyl ether/ethyl alcohol mixture. The cyclic esters were made by heating the sodium salts to 300-315°C. under reduced pressure. The butyric acid derivative was purified by distillation at 78-85°C./0.07 mm. and by crystallization

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from ethyl alcohol/petroleum ether, with cooling in solid carbon dioxide. The heptanoic acid derivative was purified by crystallization from pentane, with cooling in solid carbon dioxide, and from ethyl alcohol. Both cyclic esters were characterized by elemental analyses and infrared absorption spectra.

TABLE V

<u>Example</u>	<u>XIV</u>	<u>XV</u>
% Comonomer	11.6% Intermolecular cyclic ester of $\alpha$ -hydroxybutric acid	10% Intermolecular cyclic ester of $\alpha$ -hydroxyheptanoic acid
Inh. viscosity (bulk)	2.15	2.28
Spinning temperature	185°C.	190°C.
Draw ratio	10*	8
Drawing temperature	94°C., 122°C.*	98°C.
Inherent viscosity	1.42**	1.63**
Tensile strength (psi)	66,300	59,100
Elongation at break	22.3%	18.3%
Modulus (psi)	$1.04 \times 10^6$	$0.95 \times 10^6$
Shrinkage (H <sub>2</sub> O/77°C./5 min.)	20.6%	55.0%
Weight loss (H <sub>2</sub> O/100°C./48 hrs.)	60.5%	63.6%

\*This filament was drawn in two stages. In the first stage it was drawn 7X (draw ratio of 7) at 94°C.; in the second, it was drawn at 122°C. to an extent sufficient to give an overall draw ratio of 10.

\*\*Measured on undrawn filament. The inherent viscosities of the filaments of Examples V-XIII were measured on drawn filaments.

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EXAMPLE XVI

A mixture of 206 g. of powdered L-lactide/DL-lactide (90/10) copolymer and 0.6182 g. of the monosodium salt of 4-[4-(N-ethyl-p-sulfobenzylamino)diphenylmethylene]-[1-(N-ethyl-N-p-sulfoniumbenzyl)- $\Delta^{2,5}$ -cyclohexadienimine] [F D & C (Food, Drug, and Cosmetic) Green No. 17] was rotated in a Fisher-Kendall mixer for 48 hours at room temperature. The resulting homogeneous mixture was pressed to a plug and spun into green monofilaments by essentially the method of Example V.

Although in the examples bulk polymerization has been used in preparing the polylactides, it is to be understood that the polymerization can also be effected in solution or suspension. When the solution method is used, the ratio of monomer to solvent can be from 1:1 to 5:1. Suitable media are aromatic hydrocarbons such as the xylenes, and ethers such as tetrahydrofuran, dioxane, and 1,2-dimethoxyethane.

Although this invention has been more specifically illustrated with monofilaments, it is to be understood that the polylactic acid material can be in the form of multifilaments, e.g., braided structures as well as in the form of rods, sheets and tubes. The term "braided structure" is used to include all sutures containing more than one individual strand of a polylactide. The filaments can be braided to form useful sutures in any of a wide variety of ways such as, for example, in the manner customarily employed for making Manila rope, lanyards and the like. In the final braided suture, at least 50% of the individual strands should be oriented. Preferably 90% or more of the strands making up the braided structure should be oriented.



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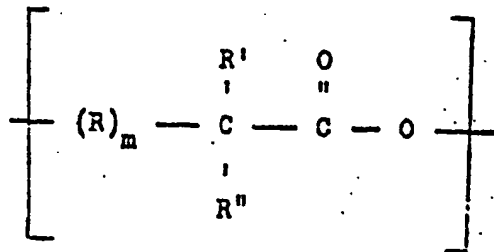
The products of the invention are useful in surgical applications where an absorbable aid or support is required, for example, in the formation of surgical mesh, absorbable staple, artificial tendons, or cartilage material, and in other uses where a temporary aid during healing is needed. They may also be used to advantage in repairing hernias and in anchoring organs which have become loose.

As many apparently widely different embodiments of this invention may be made without departing from the spirit and scope thereof, it is to be understood that this invention is not limited to the specific embodiments thereof except as defined in the appended claims.

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The claims defining the invention are as follows:-

1. An absorbable surgical suture comprising an oriented filament of a polylactide containing from zero to 15% by weight of repeating units of the formula

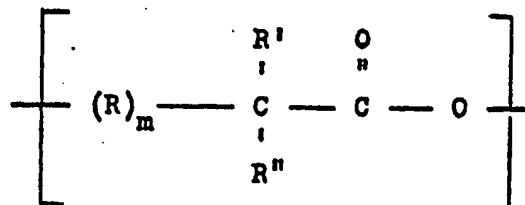


where R is lower alkylene, m is an integer of zero to 1, R' is selected from the class consisting of hydrogen and lower alkyl, and R'', which can be the same or different from R', is selected from the class consisting of hydrogen and alkyl of up to 22 carbons when m is zero and, when m is 1, R'' is selected from the class consisting of hydrogen and lower alkyl, said polylactide before being oriented being characterized by having an inherent viscosity of at least 1.0 at 0.1% concentration in benzene at 25°C. and by losing at least about 20% of its weight on treatment with boiling water for a period of 100 hours, and the filament itself being further characterized by exhibiting a tensile strength of from 25,000 psi to 100,000 psi and by having a diameter of 0.1-45 mils.

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2. A completely absorbable surgical suture consisting essentially of an oriented monofilament of a polylactide, 1-20 mils in diameter, said monofilament being oriented by drawing the filament at a temperature of 70 to 140°C. at a draw ratio of up to 11X, the polylactide from which the monofilament is prepared being characterized by containing from zero to 15% by weight of repeating units of the formula



where R is lower alkylene, m is an integer of zero to 1, R' is selected from the class consisting of hydrogen and lower alkyl, and R'', which can be the same or different from R', is selected from the class consisting of hydrogen and alkyl of up to 22 carbons when m is zero and, when m is 1, R'' is selected from the class consisting of hydrogen and lower alkyl, said polylactide prior to being oriented being characterized by having an inherent viscosity of at least 1.0 at 0.1% concentration in benzene at 25°C. and by losing at least about 20% of its weight on treatment with boiling water for a period of

100 hours. 20 APR 1965

3. The suture of claim 1 wherein the polylactide is a homopolymer of L(-)-lactide. 20 APR 1965

4. The suture of claim 1 wherein the polylactide contains up to 12% of repeating units derived from glycolide.

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5. The suture of claim 1 wherein the polylactide is poly-L(-)-lactide containing up to 15% of repeating units derived from DL-lactide.

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6. Sutures of claim 1 containing a minor amount of an inert coloring agent and plasticizer.

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7. Sutures of claim 1 containing glyceryl triacetate as a plasticizer.

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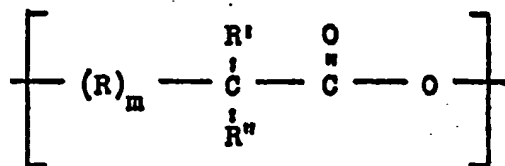
8. The suture of claim 1 wherein the polylactide is a 95/5 copolymer of L(-)-lactide and DL-lactide.

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9. In a process of suturing, the step of joining tissue with a suture of claim 1.

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10. An absorbable surgical suture in the form of a braided structure comprising filaments of a polylactide composition containing up to 15% by weight of repeating units of the formula

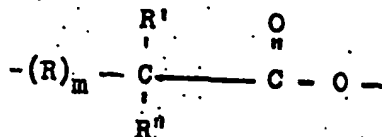


where R is lower alkylene, m is an integer of zero to 1, R' is selected from the class consisting of hydrogen and lower alkyl, and R'', which can be the same or different from R', is selected from the class consisting of hydrogen and alkyl of up to 22 carbons when m is zero and, when m is 1, R'' is selected from the class consisting of hydrogen and lower alkyl, said polylactide composition prior to being oriented being characterized by having an inherent viscosity of at least 1.0 at 0.1% concentration in benzene at 25°C.

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and by losing at least about 20% of its weight on treatment with boiling water for a period of 100 hours, at least 50% of the filaments making up the braided structure being oriented, the diameter of the filaments ranging from 0.1 mil up to 45 mils, and the braided structure itself being characterized by exhibiting a tensile strength of from 25,000 psi up to 100,000 psi 20 APR 1965

11. A process for preparing absorbable surgical sutures in accordance with Claim 1 which comprises the steps of melt-extruding a polylactic acid having an inherent viscosity of at least 1.0 at 0.1% concentration by weight in benzene at 25°C. through a spinneret having an orifice size of from about 20 to 70 mils, drawing the resulting filaments to at least four times their original length to effect orientation, and annealing the resultant oriented filaments by heating them at 60°-150°C., while held substantially taut, until they show less than 15% shrinkage on subsequent immersion, without tension, in water at 77°C., wherein as polylactic acids there are used here such polylactide compositions which contain up to about 15%, and preferably up to about 10% to 12% by weight of repeating units of the formula:



wherein R is lower alkylene, preferably methylene (-CH<sub>2</sub>-) or ethylene (-CH<sub>2</sub>CH<sub>2</sub>-), m is 0 or 1, R' is hydrogen or lower alkyl, R'' is hydrogen or alkyl of up to about 22 carbons when m is 0 and hydrogen or lower alkyl when m is 1, and can be the same as R' or different. 20 APR 1965

12. A process of Claim 11 in which the drawing step is effected at a temperature of from 80°C. to 130°C., the draw ratio being from 5:1 to 10:1. 29

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13. An absorbable surgical suture substantially as hereinbefore described with reference to the examples.

14. A process for preparing an absorbable surgical suture substantially as hereinbefore described with reference to the examples. 20 APR 1965

DATED this 18th day of April, 1966

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